PATENT SPECIFICATION

NO DRAWINGS

Inventor: ALBERTO ERCOLI

916,778

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The inventor of this invention in the sense of being the actual deviser thereof within the meaning of Section 16 of the Patents Act 1949 is ALBERTO ERCOLI an Italian Citizen of Via Circo 12, Milan, Italy.

COMPLETE SPECIFICATION

Oral Compositions containing 3-Substituted 17-α-Methyl Testosterones

ERRATA

SPECIFICATION No. 916,778

Page 2, Table, *for* "-methyltesterone-3-sec-" *read* "-methyltestosterone-3-sec-"
Page 2, line 57, *for* "gastic" *read* "gastric"
Page 2, line 70, *for* "cenonut" *read* "coconut"
Page 3, line 21, *for* "or" *read* "of"
Page 5, Table II Heading, *for* "prostrata" *read* "prostata"

THE PATENT OFFICE
23rd February 1965

of testosterone are required in order to obtain the same physiological effect. When given sublingually, doses from one half to two thirds of the oral doses are effective, but in practice sublingual administration may cause remarkable differences in absorption, especially when the tablet is not kept until it dissolves completely, either between the cheek and the gum or under the tongue without swallowing any saliva. In addition, sublingual administration is troublesome and patients do not like it owing to the bitter and disagreeable taste of the steroid.

It has now been found that the 3-enol ethers or 3-glycol-ketals of 17α-methyltestosterone are orally active hormonal agents showing androgenic and myogenic activity in excess of methyltestosterone itself.

possess generally an activity very inferior to that of the present hormone. For instance, when administered parenterally to male castrated rats they do not cause a significant increase in seminal vesicles and levator ani weights, owing to the lack of androgenic and myogenic activity.

The distinctive superiority of the oral androgenic and anabolic activity of the 3-enol ethers of 17α-methyltestosterone is shown in the table below which summarizes the pharmacological results obtained, in the usual test for the evaluation of the hormonal activity, by some representative compounds of the compositions of this invention compared with that of 17α-methyltestosterone.

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COMPLETE SPECIFICATION

Oral Compositions containing 3-Substituted 17-α-Methyl Testosterones

We, FRANCESCO VISMARA S.p.A. an Italian Body Corporate of Casatenova Brianza, Milan, Italy, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to novel hormonal compositions having enhanced physiological effect, particularly enhanced androgenic and anabolic effect and to certain new compounds for use in such compositions.

Methyltestosterone is known as an orally effective form of testosterone since it has the advantage over testosterone itself in being active when administered orally or sublingually. Therefore, methyltestosterone has resulted in a more general use of androgenic therapy, although it is less effective than the natural hormone. When orally administered, doses from 3 to 5 times as large as those of testosterone are required in order to obtain the same physiological effect. When given sublingually, doses from one half to two thirds of the oral doses are effective, but in practice sublingual administration may cause remarkable differences in absorption, especially when the tablet is not kept until it dissolves completely, either between the cheek and the gum or under the tongue without swallowing any saliva. In addition, sublingual administration is troublesome and patients do not like it owing to the bitter and disagreeable taste of the steroid.

It has now been found that the 3-enol ethers or 3-glycol-ketals of 17α-methyltestosterone are orally active hormonal agents showing androgenic and myogenic activity in excess of methyltestosterone itself.

According to the invention, therefore, there is provided an oral composition having high androgenic and anabolic activity comprising at least one 3-enol ether, as hereinafter defined, or 3-glycol ketal of 17α-methyltestosterone which may be free or esterified in the 17β-position, together with an orally ingestible pharmaceutical carrier compatible with the ether or glycol.

Prior to this invention the known 17α-methyltestosterone 3-enol ethers had never been regarded as possible hormonal agents and their usefulness had been limited to their use as intermediates for the preparation of methyltestosterone starting from Δ^4-androsten-3,17-dione.

The superior hormonal activity of the 3-enol ethers of 17α-methyltestosterone was unexpected since it was already found that in the corresponding series of testosterones not containing a 17-alkyl group, the enol ethers possess generally an activity very inferior to that of the present hormone. For instance, when administered parenterally to male castrated rats they do not cause a significant increase in seminal vesicles and levator ani weights, owing to the lack of androgenic and myogenic activity.

The distinctive superiority of the oral androgenic and anabolic activity of the 3-enol ethers of 17α-methyltestosterone is shown in the table below which summarizes the pharmacological results obtained, in the usual test for the evaluation of the hormonal activity, by some representative compounds of the compositions of this invention compared with that of 17α-methyltestosterone.

TABLE I

Test Compound	Oral androgenic activity	Oral anabolic activity
17α-methyltestosterone (standard)	1	1
17α-methyltesterone-3-*sec*-butyl enolether	2.7	1.7
17α-methyltestosterone-3-*n*-amyl enolether	3.5	2
17α-methyltestosterone-3-*iso*amylenolether	2.5	1.7
17α-methyltestosterone-3-hexyl enolether	3	1.9
17α-methyltestosterone-3-(2-methyl) pentyl enol ether	3	2.1
17α-methyltestosterone-3-*n*-heptyl enol ether	3	2.1
17α-methyltestosterone-3-cyclohexyl enol ether	2.5	1.6
17α-methyltestosterone-3-benzyl enol ether	2.5	1.8

By the term "17α-methyltestosterone 3-enol ethers" as used herein is to be understood 3-enol ethers of 17α-methyltestosterone having at the 3-position a residue of an aliphatic, alicyclic, arylaliphatic, aromatic or heterocyclic alcohol. Such residue may contain, for example, a straight or branched chain alkyl group, which may be substituted e.g. by halogen, or an alkylene group, such as ethylene, an aralkyl group, such as benzyl, a tetrahydropyranyl group, or may be a sugar residue such as that of glucose, galactose, or maltose.

The hydroxy group at the 17β-position may, as previously stated, be free or blocked in the form of an ester with an aliphatic, alicyclic, arylaliphatic, aromatic or heterocyclic carboxylic acid.

Preferred and advantageous compounds for the compositions of this invention are 3-enol alkyl or cycloalkyl ethers of free or acylated 17α-methyltestosterone. Such 3-enol alkyl or cycloalkyl ethers of free or acylated 17α-methyltestosterone having from 4 to 8 carbon atoms in the alkyl or cycloalkyl group are novel and are provided as a further feature of the invention. Particularly preferred compounds are enol alkyl ethers having at the 3-position a straight chain or from 4 to 8 atoms, if desired with methyl- or ethyl-substituents. Among the glycol ketals, the alkylene glycol ketals are preferred, particularly those containing from 2 to 4 carbon atoms in the glycol group.

The 3-enol ethers or 3-glycol ketals of 17α-methyltestosterone may be associated with any orally ingestible solid or liquid pharmaceutical carrier which is compatible with the active material. Thus the compositions of the invention may take the form of tablets, powders, capsules, syrups or other dosage forms particularly suitable for oral ingestion.

When the active material is mixed with any of the solid diluents and/or tabletting adjuvants used in pharmaceutical practice, it is advisable to stabilise such compositions by adding an alkaline substance (for example an alkaline oxide or carbonate) in order to prevent the 3-enol ethers of 17α-methyltestosterone from hydrolyzing, since these active ingredients may dissociate in an acidic medium, giving the corresponding 17α-methyltestosterone which is less effective as an oral hormone. These compositions can be also suitable coated in order to protect them from the action of gastic juice. With the same purpose in mind, the active material may be introduced, alone or mixed with suitable diluents or stabilising agents, as hereinbefore defined, into proper keratin capsules or other enteric-resistant material that acts as a solid carrier.

Preferred pharmaceutical carriers in the compositions according to the present invention are orally ingestible oils, fats, waxes, fatty acids or phospholipids of animal or vegetable origin and preferably having a high coefficient of digestibility.

Examples of suitable oils include cononut oil, corn oil, cottonseed oil, lard oil, linseed oil, olive oil, sunflowerseed oil, palm oil, peanut oil, sesame oil, soya bean oil, wheat germ oil and egg yolk oil. Suitable fats include butterfat, lard, cocoa butter and margarine fat.

Suitable carriers also include mono- and

diglycerides of animal or vegeteable origin and synthetic triglycerides, that is esters of glycerol with aliphatic acids having from 10 to 22 carbon atoms, either saturated or unsaturated, known as fat or fatty acids. Instead of glycerides, the free fatty acids contained in the fats or oils themselves can be employed.

The fatty acids may have from 10 to 22 carbon atoms. Examples of suitable fatty acids include decenoic, decosanoic, lauric, palmitic, stearic, arachidic, oleic, linoleic and linolenic acids.

The 3-enol ethers or glycol ketals of 17α-methyltestosterone are mixed with one or more of such carriers and dissolved therein, thus obtaining a lipidic composition containing the active ingredients, which is stable, homogeneous, of defined dosage form and particularly suitable for oral ingestion. Such a composition can be administered as such or preferably in the form of a capsule, e.g. or gelatine or other material soluble or disintegrateable in the alimentary tract.

The compositions can also contain some small amounts of other androgenic and/or anabolic steroid hormones. There may, if desired, be added to compositions of the present invention antiseptics, antioxidants and/or preservatives to prolong the stability of the active ingredients and prevent them from oxidizing or otherwise being degraded.

The 3-enol ethers or 3-glycol ketals of 17α-methyltestosterone are present in the compositions of this invention in an amount sufficient to produce therapeutic effects. In general, the amount is of from about 1 mg to about 50 mg. preferably from about 2.5 mg to about 30 mg per dosage unit.

The administration of the composition according to the invention is by the oral route, advantageously in equal doses of one to two or four times daily to give a daily dosage of from about 2 mg to about 100 mg and preferably from about 5 mg to about 60 mg.

The 3-enol ethers or 3-glycol ketals of 17α-methyltestosterone of the present invention can be obtained in any convenient manner. For example, one may obtain them from the corresponding 3-enol ethers or ketals of Δ^4-androstene-3,17-dione by treatment with methyl magnesium halide as Grignard reagent in order to convert the 17-keto group to a 17β-hydroxy: 17α-methyl grouping.

Alternatively, some higher alkyl or cycloalkyl enol ethers can be obtained by means of an exchange reaction which comprises heating the preformed enol ethyl ether of 17α-methyltestosterone with an excess of the desired aliphatic, or cycloaliphatic alcohol in the presence of an acid catalyst.

Other alkyl and benzyl enol ethers, especially those substituted with functional groups such as nitro and halo groups, can be more readily prepared by treatment of 17α-methyltestosterone itself with the desired alcohol (e.g. ethylene chlorohydrin or benzyl alcohol or one of the nitro-substituted aralkyl alcohols), carrying out the reaction in isooctane which on account of its high boiling point (almost identical with that of water) facilitates the course of the reaction.

In order that the invention may be well understood, the following examples are given by way of illustration only.

EXAMPLE 1

In a 3-necked flask fitted with a dropping funnel, reflux condenser, stirrer, and nitrogen inlet tube, a solution of 25 g of methyl magnesium bromide in 150 cc of ether was placed. With stirring and under an atmosphere of nitrogen, a solution of 4 g of androstendione 3-*n*-amyl enol ether in 80 cc of anhydrous benzene was added slowly.

The reaction mixture was refluxed for 1 hour and allowed to stand overnight at room temperature. The reaction mixture was then treated with an aqueous solution of 30% ammonium chloride, the organic layer separated off, washed with water and dried over anhydrous sodium sulphate.

The solvent was evaporated and the residue taken up with dilute methanol gave 3.2 g. of a white product. Crystallization from methanol containing a few drops of pyridine gave the pure methyltestosterone 3-enol *n*-amyl ether at melting point 96—98°C.

EXAMPLE 2

To a mixture of 10 g of magnesium and 160 cc of anhydrous ether, a solution of 42 g of methyl bromide in 120 cc of anhydrous ether was added slowly during a ten minute period. When the reaction with magnesium was complete 9 g of 3-enol (2-methyl)-pentyl ether of androsten-3,17-dione were added and the reaction mixture treated as in Example 1 gave 7.3 g of 3-enol (2-methyl)-pentyl ether of 17α-methyltestosterone, M.p. 85—89°C.

EXAMPLE 3

Following the same procedure as in Example 1, other representative 17α-methyltestosterones 3-enol ethers were prepared, including 3-enol *sec.* butyl ether (M.P. 131—134°C), 3-enol-isobutyl ether (M.P. 128—130°C), 3-enol heptyl ether (M.P. 62—64°C), 3-enol *sec*-(3,3-dimethyl)-butyl ether (M.P. 113—115°C), 3-enol(2-ethyl)-butyl ether (M.P. 106—107°C), and 3-enol octyl ether (M.P. 36—40°C).

EXAMPLE 4

To a suspension of 5 g of methyltestosterone in 500 cc of pure isooctane (2,2,4-trimethylpentane), 2.5 cc of benzyl alcohol and 0.25 g of *p*-toluensulphonic acid were added. The mixture was refluxed for 32 hours employing an apparatus (similar to that described in Org.Synt.*3*, page 382) equipped in such a way that the isooctane falling from the condenser before returning to the flask was separated from the water entrained by it by

means of a trap supplied with an inner funnel containing phosphorus pentoxide mixed with a filter aid. After cooling, few drops of pyridine were added and the solvent completely evaporated in vacuo to dryness. The solid residue, recrystallised from methanol containing a little pyridine, gave 2.5 g of 3-enol benzyl ether of 17α-methyltestosterone, M.P. 132—135°C.

EXAMPLE 5

Following the same procedure as in Example 4 and substituting benzyl alcohol for ethylene chlorohydrin, the 3-enol chloroethyl ether of 17α-methyltestosterone was obtained at melting point 120—122°C.

EXAMPLE 6

To a solution of 3 g. of 17α-methyltestosterone acetate in 20 cc of tetrahydrofuran, 3 cc of ethyl orthoformate and 20 mg of *p*-toluensulphonic acid was added. The reaction mixture was allowed to stand at room temperature for a two hours period, then neutralized with little pyridine. The product which precipitated was filtered off, dried and recrystallized from methyl alcohol. The pure 3-enol ethyl ether of 17α-methyltestosterone acetate was obtained at M.P. 132—133°C.

EXAMPLE 7

To 600 cc of anhydrous benzene, 0.15 g of *p*-toluene sulphonic acid were added and a portion of the solvent was distilled off azeotropically to remove any possible trace of moisture. A mixture of 6 cc of *n*-hexyl alcohol and 3 g of 3-enol ethyl ether of 17α-methyltestosterone was added and distillation was continued again for about 30 minutes, so that the ethyl alcohol which formed during the reaction was completely removed.

To the residual solution, a few drops of pyridine were added and the mixture concentrated under vacuum. The residue taken up with ether, filtered, dried and then recrystallized from methanol containing a trace of pyridine to give 3-enol *n*-hexylether of 17α-methyltestosterone, M.P. 79—81°C.

EXAMPLE 8

10 g of 3-enol ethyl ether of 17α-methyltestosterone were dissolved in about 800 cc of anhydrous benzene and treated with a mixture of 1.2 g of *p*-toluensulphonic acid and 18 cc of cyclohexanol. The reaction mixture was processed as in Example 7 to give 3-enol-cyclohexylether of 17α-methyltestosterone, M.P. 142—144°C.

EXAMPLE 9

50 g of 3-enol *n*-amyl ether of 17α-methyltestosterone, ground to a fine powder (preferably micronized), were suspended in a two litre mixture of sesame oil and olive oil. The mixture was carefully heated on a water bath with occasional shaking of the suspension so as to obtain a clear and homogeneous solution. After cooling, the solution was introduced into soft gelatin capsules of 0.8 cc each, so that each contained about 20 mg of 3-enol *n*-amyl ether of 17α-methyltestosterone. The capsules provided a stable pharmaceutical composition for oral use, very effective in its therapeutic properties.

EXAMPLE 10

28 g of 3-enol (2-methyl)-pentyl ether of 17α-methyltestosterone were admixed with 2.5 litres of sunflowerseed oil containing propyl gallate in the proportion of 8 mg/litre. The mixture was heated on a water bath, the suspension being occasionally shaken and the temperature slowly raised until dissolution was complete. The clear and homogeneous solution was transferred into 0.8 cc capsules so that each capsule contained about 9 mg of 3-enol (2-methyl)-pentyl ether of 17α-methyltestosterone.

EXAMPLE 11

Pharmacological testing

The hormonal activity of some representative 17α-methyl-testosterone 3-enol ethers of the compositions of this invention was evaluated by comparison with that of methyltestosterone on the assay for androgenic and myogenic activity performed according to Hershberger et al. (Proc. Soc. Exp. Biol. Med. *83*, 175, 1953).

Male albino rats, initial weight 40—45 g, maintained on standard diet were used. The animals were castrated under ether anaesthesia and the oral treatment with the test compounds in 0.2 cc sesame oil solution started on the day of castration and lasted for seven consecutive days.

The animals were killed during the 8th day and the weights of ventral prostata, levator ani muscle and seminal vesicles, without coagulating glands and devoid of fluid, were determined to the nearest 0.5 mg. From the data reported in Table II below, it appears that the 3-enol ethers of 17α-methyltestosterone, administered orally at equivalent doses, show a greater and statistically significant action than the oral 17α-methyltestosterone.

TABLE II

Treatment	Daily Dose (mg)	Organ weight (mg/100 g body weight)		
		seminal vesicles	Ventral prostrata	Levator ani
17α-Methyltestosterone	0.302	11.3 ± 0.6	48.1 ± 3.0	24.2 ± 1.6
	0.604	17.2 ± 1.0	75.5 ± 2	37.4 ± 1.5
17α-Methyltestosterone 3-*n*-amylenolether	0.186	24.8 ± 2.0	75.4 ± 4.0	35.9 ± 2.5
	0.372	41.0 ± 2.4	106.0 ± 5.5	47.5 ± 3.0
17α-Methyltestosterone 3-*n*-hexylenolether	0.193	23.2 ± 1.4	69.3 ± 4.3	35.9 ± 1.8
	0.386	24.0 ± 2.3	86.8 ± 6.8	38.9 ± 1.5
	0.772	44.8 ± 2.7	116.8 ± 8.3	54.3 ± 3.3
17α-Methyltestosterone 3-benzylenolether	0.392	27.4 ± 2.6	93.6 ± 8.0	43.4 ± 2.8
	0.784	51.7 ± 3.2	135.5 ± 11.9	67.0 ± 4.2
17α-Methyltestosterone 3-cyclohexylenolether	0.384	35.9 ± 2.0	100.3 ± 4.5	49.2 ± 2.2
	0.768	42.5 ± 2.2	103.6 ± 5.7	57.2 ± 1.9
17α-Methyltestosterone 3-*n*-butylenolether	0.716	33.7 ± 3.2	93.6 ± 5.0	47.9 ± 3.8
17α-Methyltestosterone 3-*iso*-butylenolether	0.716	32.9 ± 2.4	95.6 ± 3.7	44.4 ± 3.4
17α-Methyltestosterone 3-*sec.*butylenolether	0.716	46.7 ± 1.0	124.5 ± 4.5	62.4 ± 3.2
17α-Methyltestosterone 3-ethylenolether	0.660	31.0 ± 2.7	92.7 ± 6.3	53.2 ± 2.0
17α-Methyltestosterone 3-chloroethylenelether	0.718	27.7 ± 2.0	104.0 ± 7.7	53.0 ± 3.0
17α-Methyltestosterone 3-glycolketal	0.692	26.4 ± 2.9	102.8 ± 5.4	46.6 ± 2.6

EXAMPLE 12

An oral composition was prepared with the following components:

17α-Methyltestosterone 3-enol hexyl ether	5 mg
Magnesium stearate	25 mg
Magnesium oxide	20 mg
Lactose	200 mg

The above ingredients were screened, mixed and filled into hard gelatin capsules.

EXAMPLE 13

Tablets were prepared with the following ingredients:

17α-Methyltestosterone 3-enolbenzyl ether	15 mg
Rice starch	20 mg
Lactose	50 mg
Talc	10 mg
Calcium carbonate and magnesium oxide	35 mg
Sugar coating, approximately	50 mg

EXAMPLE 14

Soft gelatin capsules were prepared containing from about 2.5 mg to about 25 mg of 17α-methyltestosterone 3-enol *n*-heptyl ether in one ml. of peanut oil. These capsules provided an oral hormonal composition which is satisfactory for clinical use.

EXAMPLE 15

A mixture of 8 g of 17α-methyltestosterone 3-enol *iso*-butyl ether and 7 g of 17α-methyltestosterone 3-enol *sec*-butyl ether was dissolved by gently heating in 500 cc of corn oil and wheat germ oil (1:1) solution and filled into soft gelatin capsules.

EXAMPLE 16

In the same manner as in Example 9, 10 lipidic oral compositions of 3-enol cyclohexyl ether of 17α-methyltestosterone were prepared by using sesame oil, olive oil and sunflower-seed oil singly or in admixture as liquid carriers.

WHAT WE CLAIM IS:—

1. An oral composition having high androgenic and anabolic activity comprising at least one 3-enol ether, as herein defined, or 3-glycol ketal of 17α-methyltestosterone, which may be free or esterified in the 17β-position, together with an orally ingestible pharmaceutical carrier compatible with the ether or glycol.

2. An oral composition as defined in claim 1 in which said 3-enol ether of 17α-methyltestosterone is a straight or branched chain alkyl enol ether.

3. An oral composition as defined in claim 1 in which said 3-enol ether of 17α-methyltestosterone is a cycloalkyl enol ether.

4. An oral composition as defined in claim 1 in which said 3-enol ether of 17α-methyltestosterone is an aralkyl enol ether.

5. An oral composition as defined in claim 1 in which the pharmaceutical carrier comprises at least one orally ingestible oil, fat, wax, fatty acid or phospholipide of animal or vegetable origin.

6. An oral composition as defined in claim 5 in which said oil or fat has a high coefficient of digestibility.

7. An oral composition as defined in claim 5 in which said pharmaceutical carrier is a fatty acid having from 10 to 22 carbon atoms or a glyceride of such fatty acid.

8. An oral composition as defined in claim 1 in which said pharmaceutical carrier is a synthetic triglyceride of a fatty acid having from 10 to 22 carbon atoms.

9. A composition for oral use as claimed in claim 5 or claim 8 said composition being contained in a capsule composed of material soluble or disintegreable in the alimentary tract.

10. An oral composition as claimed in any of the preceding claims in which the 3-enol ether or glycol ketal of 17α-methyltestosterone is used in an amount of from 1 to 50 mg.

11. Compositions for oral use as claimed in claim 1 substantially as herein described with reference to any of examples 9—16.

12. The 3-enol alkyl or cycloalkyl ethers of free or acylated 17α-methyltestosterone having from 4 to 8 carbon atoms in the alkyl or cycloalkyl group.

13. Compounds as claimed in claim 12 specifically as disclosed in any of examples 1, 2, 3, 7 or 8.

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